REMARKS

Claims 58-108 are pending in this application. Claims 105 and 106 have been amended in the instant amendment to more particularly point out and distinctly claim that which Applicants consider their invention. Support for amended claims 105 and 106 is found within the claims as originally filed and in the Specification. No new matter has been added.

The Examiner contends that this Application contains the following groups of inventions, which allegedly are not so linked as to form a single inventive concept under PCT Rule 13.1:

Group I, claims 58-89, 92-97, and 105-108, drawn to bispecific chimeric molecule and conditional system for expression; and

Group II, claims 90, 91, and 98-104, drawn to nucleic acid encoding a bispecific chimeric molecule, vector, and pharmaceutical composition.

The Examiner alleges that the inventions listed as Groups I and II do not share a special technical feature and has required restriction under 35 U.S.C. §§ 121 and 372. In reply, and solely to be responsive to the Examiner's requirement, Applicants provisionally elect Group I, claims 58-89, 92-97, and 105-108, with traverse. Applicants submit that the claims of Groups I and II are drawn to a single invention, and are properly considered together. Applicants respectfully request reconsideration of the Requirement for Restriction under 37 C.F.R. § 1.143, or in the alternative, modification of the Restriction Requirement to allow prosecution of more than one group of claims designated by the Examiner in the present Application in light of the following remarks.

On page 4 of the Office Action, the Examiner requires the election of a species, which comprises one specific domain for each of the generic domains recited in generic claims 58. 90-92, 98, and 103. Within the elected Group I claims, Applicants provisionally elect an ScFv-tag-Hinge-TetR from N-terminal domain to C-terminal domain species, with traverse. Consistent with Applicants' provisional species election, Applicants also provisionally elect the following:

- antibody fragment within claim 72;
- SEQ ID NO:5 within claim 77;
- SEQ ID NO: 7 for the tag peptide sequence, SEQ ID NO: 5 for the peptide arm, and the TetR protein DNA binding domain within claim 80;

- TATA box within claim 95; and
- protein having transcriptional transactivating activity of claim 105.

Pending claims 58, 61-63, 65, 66, 72, 74-77, 79, 80, 92, 93, 95-97, and 105-107 read upon the Applicants' provisionally elected species. Applicants submit that the species of the invention are drawn to a single inventive concept, and are properly considered together.

Applicants respectfully request reconsideration of the Requirement for Restriction under 37 C.F.R. § 1.143, or in the alternative, modification of the Restriction Requirement to allow prosecution of more than one group of claims designated by the Examiner in the present Application, for the following reasons.

In this case, the appropriate standard for restriction is under the unity of invention criteria of the PCT. Applicants have the right to include in a single application those inventions so linked as to form a single general inventive concept. MPEP § 1893.03(d). Unity of invention exists when there is a technical relationship among the claimed inventions involving one or more special technical features, meaning those technical features that define a contribution which each of the inventions considered as a whole, makes over the prior art. MPEP § 1893.03(d).

Claims 58-108 Are Drawn To A Single Inventive Concept And Share A Special Technical Feature

Applying the appropriate criteria in the instant application, Applicants note that the special technical feature of the claims of the instant application is the bispecific chimeric molecule of independent claim 58. The remaining claims, 59-103 and 105-108, all depend directly or indirectly from independent claim 58, except independent claim 104. However, claim 104 relates to an isolated nucleic acid comprising a sequence as depicted in SEQ ID No. 4, which is a 768 base pair cDNA encoding the VH-L-VL chain, which is used to construct the bispecific chimeric molecule of independent claim 58 (see page 15, line 13 to page 16, line 12 and Example 2 of the Specification). Therefore, all of pending claims 58-108 share the special technical feature of the bispecific chimeric molecule.

Few inventions are in closer relationship than a protein (or polypeptide) and the nucleic acid encoding that protein. The nucleic acid contains the genetic code for the encoded protein, and although due to the degeneracy of the genetic code more than one nucleic acid may encode the same protein, the intimate relationship between nucleic acid and the encoded protein is apparent. Indeed, the MPEP

defines that a protein and a DNA sequence encoding that protein exhibit corresponding technical features, whereby unity of the invention between the protein and the DNA sequence exist (see MPEP, Annex B, Part 2, Example 17). Accordingly, the inventions represented by Group I and Group II are not independent. It also follows that vectors comprising the nucleic acids encoding the bispecific chimeric molecule of Group I and a pharmaceutical composition comprising a vector of the invention of Group II are also not independent from Group I.

Applicants respectfully submit that claims 58-108 are drawn to a single general inventive concept as defined in PCT Rule 13.1, and comprise the same or corresponding special technical features as defined under PCT Rule 13.2. Specifically, Applicants submit that claims 58-89, 92-97, and 105-108 (Group I) include subject matter directed to bispecific chimeric molecules. The claims of Group II (claims 90, 91, and 98-104) are directed to nucleic acids encoding the bispecific chimeric molecules of Group I and vectors and a pharmaceutical composition comprising a vector encoding a bispecific chimeric molecule of Group I. The subject matter of Group II is clearly related to the subject matter of Group I. Indeed, all Group II claims depend directly or indirectly from claim 58 (Group I), except claim 104, which, as discussed above, relates to an isolated nucleic acid comprising a sequence as depicted in SEQ ID No. 4, which is used to construct the bispecific chimeric molecule of independent claim 58 (Group I). Indeed, the claims of Groups I and II share special technical features. This special technical feature is the bispecific chimeric molecule itself. Accordingly, the claims of Groups I and II are linked as to form a single general inventive concept under 37 CFR § 1.475 and PCT Rule 13.1.

Applicants respectfully submit that, contrary to the Examiner's contention (page 2, Office Action), the claims of Groups I and II are directed to related structural, biochemical, and functional subject matter as discussed above. More particularly, these claims revolve around the novel bispecific chimeric molecules of the invention. Accordingly, modification of the Requirement for Restriction and examination of claims 58-108 is believed to be in order and is earnestly requested.

Examination Of Claims 58-108 Does Not Present Undue Burden On The Examiner

Applicants respectfully submit that prosecution of both groups of claims designated by the Examiner is appropriate. Under Patent Office examining

procedures, "[i]f the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct or independent inventions" (MPEP 803, Rev. 8, May 1988) (emphasis added). In the Office Action, the Examiner has not even averred that the groups fall into different classifications. Applicants submit that the groups designated by the Examiner fail to define products with biological properties so distinct as to warrant separate examination and search. The present claims represent a web of knowledge and continuity of effort that merits examination in a single application.

Accordingly, Group II nucleic acids, vectors, and pharmaceutical composition are related to the claimed bispecific chimeric molecules and conditional systems for expression of Group I. Thus, all of these claims involve a fundamental determination of the novelty of the bispecific chimeric molecule of Group I. To the extent that this determination would be made, it is submitted that a preponderantly coextensive search would result. In particular, an exhaustive search for the bispecific chimeric molecules and conditional systems for expression of Group I would encompass the art disclosing nucleic acids encoding the bispecific chimeric molecule, vectors comprising the bispecific chimeric molecule encoding nucleic acid, and pharmaceutical composition comprising the bispecific chimeric molecule (Group II). Similarly, a search for the nucleic acids encoding the bispecific chimeric molecule, vectors comprising the bispecific chimeric molecule encoding nucleic acid, and pharmaceutical composition comprising the bispecific chimeric molecule would reveal information about the bispecific chimeric molecules and conditional expression systems of Group I. Indeed, performing the entire search covering the bispecific chimeric molecules and conditional expression systems and their related nucleic acids, vectors, and pharmaceutical composition is less burdensome on the Examiner than separate searches, which necessarily involve duplication of searching efforts.

Applicants submit herewith Exhibit A, which is a copy of the International Search Report for application PCT/FR96/00477, in which all of the pending claims were searched together. Exhibit A is evidence that a search covering all of the pending claims 58-108 can be made without undue burden on the Examiner.

Thus, Applicants submit that the search and examination of the entire Application can be made without serious burden. Applicants respectfully submit that conjoint examination and inclusion of all of the claims of the present Application would not present an undue burden on the Examiner and, accordingly, withdrawal of the Requirement for Restriction is believed to be in order.

Conclusion

Applicants respectfully submit that claims 58-108 are drawn to a single general inventive concept as defined in PCT Rule 13.1 and comprise the same or corresponding special technical features as defined under PCT Rule 13.2. Thus, the inventions of Groups I and II, as defined by the Examiner, are not independent, and even if they might be classified in different classes for searching purposes, the search of the claims of these groups, including the claims for bispecific chimeric molecules, conditional systems for expression, nucleic acids encoding the bispecific chimeric molecules, vectors comprising a nucleic acid encoding the bispecific chimeric molecule, and a pharmaceutical composition comprising a vector comprising a nucleic acid encoding the bispecific chimeric molecule, does not impose an undue search burden on the Examiner.

Applicants submit respectfully that the Examiner has provided insufficient reasons in support of a restriction between the claims of Groups I and II. In view of the above remarks, Applicants respectfully request reconsideration and withdrawal of the finding of lack of unity between the claims of Group I and Group II. All of the claims should fairly be examined in a single application. In the event that the restriction requirement is maintained, Applicants reserve the right to file Divisional Applications directed to the subject matter of the non-elected claims of Group II. If a telephone interview would be of assistance in advancing prosecution of this application, Applicants invite the Examiner to contact their attorney, Ross J. Oehler, at (610) 454-3883.

Respectfully submitted,

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APPENDIX
U.S. Patent Application Serial No. 08/930,480
"Conditional Expression System"
RPR File No. ST95021-US
Pending Claims

58. A bispecific chimeric molecule comprising a DNA bending domain capable of binding selectively to a defined DNA sequence and a regulatory domain capable of binding specifically to a transactivator, a transrepressor or a transactivating or transrepressing complex characteristic of a physiological or physiopathological state, wherein the chimeric molecule allows the selective recruitment of a transcriptional factor or complex whose activation or inactivation leads to a physiopathological situation, or any endogenous molecule or molecule of infectious origin whose presence or absence leads to a physiopathological situation.

59. The molecule according to claim 58, wherein the domain capable of binding selectively to a defined DNA sequence is derived from a eukaryotic protein.

60. The molecule according to claim 59, wherein the domain capable of binding selectively to a defined DNA sequence is derived from a protein selected from the group consisting of p53, a STAT protein, and an NFkB protein.

61. The molecule according to claim 58, wherein the domain capable of binding selectively to a defined DNA sequence is derived from a prokaryotic protein.

62. The molecule according to claim 61, wherein the prokaryotic protein is a bacterial repressor.

63. The molecule according to claim 61, wherein the domain capable of binding selectively to a defined DNA sequence is derived from a TetR protein.

64. The molecule according to claim 61, wherein the domain capable of binding selectively to a defined DNA sequence is derived from a Cro protein.

65. The molecule according to claim 58, wherein the domain capable of binding selectively to a defined DNA sequence consists of a full length protein.

66. The molecule according to claim 65, wherein the domain capable of binding selectively to a defined DNA sequence consists of a full length TetR protein.

67. The molecule according to claim 65, wherein the domain capable of binding selectively to a defined DNA sequence consists of a full length Cro protein.

68. The molecule according to claim 58, wherein the domain capable of binding specifically to the transactivator, the transrepressor or the transactivating or transrepressing complex is an oligomerizing domain.

69. The molecule according to claim 68, wherein the oligomerizing domain is selected from the group consisting of a leucine zipper, an SH3 domain, and an SH2 domain.

70. The molecule according to claim 68, wherein the oligomerizing domain capable of binding specifically to the transactivator consists of the C-terminal part of a p53 protein having an amino acid sequence as depicted in SEQ ID No. 3.

71. The molecule according to claim 58, wherein the domain capable of binding specifically to the transactivator, the transrepressor or the transactivating or transrepressing complex is a synthetic domain known to interact with the transactivator, the transrepressor or the transactivating or transrepressing complex.

72. The molecule according to claim 58, wherein the domain capable of binding specifically to the transactivator, the transrepressor or the transactivating or transrepressing complex is an antibody or an antibody fragment or derivative directed against the transactivator, the transrepressor or the transactivating or transrepressing complex.

73. The molecule according to claim 72, wherein the domain capable of binding specifically to the transactivator or the transactivating complex consists of a Fab or F(ab)'2 fragment of the antibody or a VH or VL region of the antibody.

74. The molecule according to claim 72, wherein the domain capable of binding specifically to the transactivator or the transactivating complex consists of a single-chain antibody (ScFv).

75. The molecule according to claim 58, wherein the DNA-binding domain and the transactivator-binding domain are linked to each other through an arm consisting of from 5 to 30 amino acids.

76. The molecule according to claim 75, wherein the arm consists of 5 to 20 amino acids.

77. The molecule according to claim 76, characterized in that the arm is chosen from a peptide sequence selected from the group consisting of SEQ ID No. 5 and SEQ ID No. 6.

78. The molecule according to claim 58, wherein the DNA-binding domain is situated at the N-terminal position and the transactivator-binding domain is situated at the C-terminal position.

79. The molecule according to claim 58, wherein the DNA-binding domain is situated at the C-terminal position and the transactivator-binding domain is situated at the N-terminal position.

80. The molecule according to claim 58, wherein the molecule comprises in order from the N-terminal position to the C-terminal position: a transactivator-binding domain consisting of a single chain antibody (ScFv), a tag peptide sequence comprising SEQ ID Nos. 7 or 8, a peptide arm sequence comprising SEQ ID Nos. 5 or 6, and a DNA-binding domain consisting of a TetR or Cro protein.

81. The molecule according to claim 58, wherein the molecule comprises in order from the N-terminal position to the C-terminal position: a transactivator-binding domain consisting of a single chain antibody (ScFv), a peptide arm sequence comprising SEQ ID Nos. 5 or 6 and a DNA-binding domain consisting of a TetR or Cro protein.

82. The molecule according to claim 58, wherein the molecule comprises in order from the N-terminal position to the C-terminal position: a transactivator-binding domain consisting of a single chain antibody (ScFv), and a DNA-binding domain consisting of a TetR or Cro protein.

83. The molecule according to claim 58, wherein the molecule comprises in order from the N-terminal position to the C-terminal position: a DNA-binding domain consisting of a TetR or Cro protein and a transactivator-binding domain consisting of a single chain antibody (ScFv).

84. The molecule according to claim 58, wherein the molecule comprises in order from the N-terminal position to the C-terminal position: a DNA-binding domain consisting of a TetR or Cro protein, a peptide arm sequence comprising SEQ ID Nos. 5 or 6 and a transactivator-binding domain consisting of a single chain antibody (ScFv).

85. The molecule according to claim 58, wherein the molecule comprises in order from the N-terminal position to the C-terminal position: a domain for oligomerization comprising SEQ ID No. 3, a tag sequence comprising SEQ ID Nos. 7 or 8, a peptide arm sequence comprising SEQ ID Nos. 5 or 6, and a DNA-binding domain consisting of a TetR or Cro protein.

86. The molecule according to claim 58, wherein the molecule comprises in order from the N-terminal position to the C-terminal position: a

domain for oligomerization comprising SEQ ID No. 3, a peptide arm sequence comprising SEQ ID Nos. 5 or 6 and a DNA-binding domain consisting of a TetR or Cro protein.

87. The molecule according to claim 58, wherein the molecule comprises in order from the N-terminal position to the C-terminal position: a domain for oligomerization comprising SEQ ID No. 3 and a DNA-binding domain consisting of a TetR or Cro protein.

88. The molecule according to claim 58, wherein the molecule comprises in order from the N-terminal position to the C-terminal position: a DNA-binding domain consisting of a TetR or Cro protein and a domain for oligomerization comprising SEQ ID No. 3.

89. The molecule according to claim 58, wherein the molecule comprises in order from the N-terminal position to the C-terminal position: a DNA-binding domain consisting of a TetR or Cro protein, a peptide arm sequence comprising SEQ ID Nos. 5 or 6, and a domain for oligomerization comprising SEQ ID No. 3.

90. An isolated nucleic acid encoding a chimeric molecule according to claim 58.

91. The nucleic acid according to claim 90, wherein the nucleic acid is DNA.

92. A conditional system for the expression of a gene comprising:

(a) the bispecific chimeric molecule as defined in claim 58, and

(b) an expression cassette comprising a regulatory sequence, a minimal transcriptional promoter and a gene, wherein the bispecific chimeric molecule binds to the regulatory sequence whereby transcription activation occurs.

93. The conditional system according to claim 92, wherein the DNA-binding domain of the chimeric molecule is represented by all or part of TetR protein and a regulatory sequence comprises the sequence as depicted in SEQ ID No. 1.

94. The conditional system according to claim 92, wherein the DNA-binding domain of the chimeric molecule is represented by all or part of Cro protein and the regulatory sequence comprises a sequence as depicted in SEQ ID No. 2.

95. The conditional system according to claim 92, wherein the minimal promoter comprises an INR or a TATA box.

96. The conditional system according to claim 92, wherein the minimal promoter is derived from the promoter of a thymidine kinase gene.

97. The conditional system according to claim 92, wherein the minimal promoter is derived from the promoter of human CMV.

98. A vector comprising:

(a) a nucleic acid sequence encoding the bispecific chimeric molecule according to claim 58, and

(b) an expression cassette comprising a regulatory sequence, a minimal transcriptional promoter and a coding sequence of interest, wherein the bispecific chimeric molecule binds to the regulatory sequence whereby transcription activation occurs.

99. The vector according to claim 98, wherein a DNA-binding domain of the chimeric molecule is represented by all or part of TetR protein and the regulatory sequence comprises a sequence as depicted in SEQ ID No. 1.

100. The vector according to claim 98, wherein the DNA-binding domain of the chimeric molecule is represented by all or part of Cro protein and the regulatory sequence comprises a sequence as depicted in SEQ ID No. 2.

101. The vector according to claim 98, wherein the coding sequence of interest encodes a therapeutic product.

102. The vector according to claim 101, wherein the therapeutic product is toxic to a cell in which it is expressed.

103. A pharmaceutical composition comprising the vector according to claim 98 and a pharmaceutically acceptable vehicle.

104. An isolated nucleic acid comprising a sequence as depicted in SEQ ID No. 4.

105. (Amended) The molecule according to claim 58, wherein the transactivator complex characteristic of a physiological or physiopathological state is a protein having a transcriptional transactivating activity.

106. (Amended) The molecule according to claim 105, wherein the transactivator complex is a cellular protein.

107. The molecule according to claim 106, wherein the cellular protein is a p53 protein.

108. The molecule according to claim 58, wherein the transactivator or transactivating complex characteristic of a physiological or physiopathological state is a protein appearing in an infected or hyperproliferative cell.